amendments is found in the Specification, for example at page 6, lines 17, 18 and 20, page 12, line 12, and page 32, line 13. Therefore, no new matter has been added and entry of the amendment is respectfully requested.

The Sequence Listing

The Office Action asserts that the application fails to comply with the requirements of 37 CFR 1,821 through 1.825 for failure to provide a Sequence Listing as set forth in 37 CFR 1,821(a)(1) and (a)(2). To comply with the requirements of the statute and the Notice To Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures received herein, Applicants submit herewith a Sequence Listing, a copy of the sequence information in computer readable form, and a Statement Under 37 C.F.R. § 1.821(f) and (g) that the enclosed Sequence Listing includes no new matter. Applicants request entry of the Sequence Listing in the application following the claims on page 69 and before the Drawings. Please insert the Sequence Listing beginning with page 1 and numbering consecutively thereafter.

The Drawings

Applicant will submit formal drawings upon allowance of the pending claims.

The Rejection under 35 U.S.C. §101

Claims 1-8 stand rejected under 35 U.S.C. §101 because the claimed invention is allegedly not supported by either a credible and substantial asserted utility or a well established utility. Applicant respectfully traverses this rejection.

Specifically, the Office Action alleges that the specification does not set forth any substantial and credible utility for the products produced by the methods contained in claims 1-6, the vector in claim 7 or the polypeptide product of claim 8.

The present invention provides methods for producing mutant polynucleotides, as defined by amended claim 1, by blocking or interrupting a polynucleotide synthesis or amplification process in a recombinant cell system by treating the cell system with one or more agents that block or interrupt polynucleotide synthesis or amplification process to provide a plurality of different recombinant polynucleotides due to said polynucleotides being in various states of synthesis or amplification and subjecting one or more of the recombinant polynucleotides obtained from the cells to an amplification procedure. As the cell system is *treated* (i.e., by the hand of man) with the one or more agents that block or interrupt polynucleotide synthesis or amplification, the invention method is clearly not a naturally occurring process.

In another embodiment the invention, as defined by amended claim 2, provides methods for producing a recombinant polynucleotide encoding a polypeptide having a desired property by producing a plurality of different polynucleotides by blocking or interrupting a polynucleotide synthesis or amplification process using one or more of such agents so as to provide a plurality of different single or double-stranded polynucleotides; denaturing the plurality of different single or double stranded polynucleotides to produce a mixture of single-stranded polynucleotides; incubating all or part of the single stranded polynucleotides with a polymerase under conditions which result in annealing of the single-stranded polynucleotides at regions of identity so as to form mutagenized double stranded polynucleotides; and expressing at least one mutant polypeptide from the mutagenized double stranded polynucleotides that has a desired characteristic.

The invention methods provides an original, non-natural means of generating a plurality of different mutagenized double stranded polynucleotides from a template polynucleotide that can be used to obtain a mutant polypeptide (e.g., one not found in nature as a wild-type) possessing a desired characteristic. For example, the mutagenized double-stranded polynucleotides can be inserted into vectors and expressed as polypeptides

that can be assayed to identify those having altered function, such as greater enzymatic activity at a particular pH, or increased thermostability.

Those of skill in the art understand the importance of natural homologous recombination. In sexually reproducing organisms this occurs during meiosis when double stranded DNA divides and one strand of the original double stranded molecule recombines with another single strand (i.e., provided by another organism). This process of natural 'genetic shuffling' provides a method for increasing genetic diversity that aids in adaptation and survival.

Similarly, in the invention methods, as defined by amended claims 1 and 2, a non-natural method is provided by which the sequences of single stranded polynucleotides may be 'shuffled, 'resulting in genes that encode polypeptides with enhanced or novel characteristics.

Applicant respectfully submits that a process that allows one skilled in the art to generate mutations in a protein, which mutations may lead to enhanced function, has well established utility. Several recent articles document the usefulness of random mutagenesis, a crude method of introducing mutation, and show how such a method can create proteins with enhanced characteristics over the corresponding wild-type protein. See Engineering Human DNA Alkyltransferases for Gene Therapy Using Random Sequence Mutagenesis, Encell, et al., CANCER RESEARCH 58, 1013-1020, March 1, 1998; see also Engineering of a Cold-Adapted Protease by Sequential Random Mutagensis and a Screening System, Taguchi et al., APPL. ENVIRON. MICROBIOL. 1998 Feb. 64:2; 492-5; copies of the references are attached hereto for the Examiner's convenience. Both publications are subsequent to the earliest priority date of the present application.

The present invention discloses a recombinant method for shuffling homologous regions within and between genes. Accordingly, the invention provides

methods for producing polynucleotides that express mutant polypeptides that can be screened to detect altered function as compared to the corresponding wild-type (wt) counterpart. Such altered function may be increased thermostability, greater structural integrity, and the like. Such a method has practical importance to the biotechnology community for generating proteins, particularly enzymes, that are more stable than their wild-type counterparts for use in commercial manufacturing processes, which are typically conducted under conditions that denature protein structure or otherwise alter protein function.

Therefore, Applicant respectfully submits that the present invention, as defined by amended claims 1 and 2, sets forth a substantial and credible utility under 35 U.S.C. § 101.

In view of the above amendments and remarks, reconsideration and favorable action on claims 1-10 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: 10/24/00

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Enclosures:
- Statement re Sequence Listing
- Sequence Listing
- Computer Readable Copy of Sequence Listing
- References (2)